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# Compression characteristics of granulated materials. III. The relationship between air permeability and mechanical strength of tablets of some lactose granulations

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## Summary

Lactose was granulated with 5% by weight polyvinylpyrrolidone as binder by a wet massing-screening procedure. 14 granulations were produced by varying the amount and type of solvent for the binder during the wet massing. The size fraction 500–710 $\mu$m was prepared for each granulation and tablets were compacted in an instrumented single-punch press at 150 MPa. The tablets were then stored for 2 days at 40% relative humidity and the tensile strength was measured. Generally, the tablet strength increased with increased amount of agglomeration liquid except for the lowest amount of liquid which showed a somewhat higher tablet strength than expected from the general trend. It is suggested that this is primarily due to an increased amount of binder in these granulations. The type of binder solvent also affected the tablet strength but to a smaller extent. The air permeability compaction-pressure profiles for these granulations have been studied earlier and were here compared with the tablet strength data. Generally, the changes in tablet strength were related to variations in the degree of granule fragmentation in the different granulations. The results therefore indicate that the degree of fragmentation of the granules during compression is of significant importance for the tablet strength.

## Introduction

Granulation is a common process in the pharmaceutical industry, used primarily to prepare a powdered material for tableting. Despite the extensive use of granulated materials during tablet manufacture, there appears to be a lack of systematic research concerning how the properties of granules affect the mechanical strength of the tablets. A better understanding of the relationship between granule properties and tablet strength makes a rational optimisation of the granulation process possible, e.g. adequate tableting properties with a low amount of binder in the formulation could be obtained and problems during scaling-up and production predicted.

The first step to improve the compactibility of a material, i.e. the ability of the powder mass to form a compact of a certain strength (Leuenberger, 1982), is usually to add a binder. The effect of type and amount of binder on the tablet

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strength (e.g. Armstrong and Morton, 1977; Alderborn and Nyström, 1984) as well as important properties of the binder (e.g. Krycer et al., 1983; Reading and Spring, 1984; Cutt et al., 1986) have been discussed in the literature. However, for each specific formulation, different granulation procedures can result in different tableting properties of the mass (e.g. Rue et al., 1980; Ragnarsson and Sjögren, 1982; Alderborn et al., 1987). Consequently, besides the composition of the granulation, the physical properties of the granules might also affect the tablet strength.

During tableting of some paracetamol granulations, it was found (Rue et al.,1980) that different granulation equipment gave tablet masses with different compactibilities. It was suggested that the tablet strength was governed by the amount of binder participating in the intergranular attractions. Such differences in intergranular binder to binder contact were determined by the intragranular binder distribution and it was suggested that a peripheral binder distribution in the granules gave the best compactibility.

It has also been shown (Alderborn et al., 1987) that the composition of the binder solvent influenced the strength of tablets of a high dosage drug, wet-granulated in a high shear mixer. The tensile strength of obtained tablets increased markedly by changing the ratio of ethanol to water in the binder solvent used during the granulation process. It was suggested that the degree of fragmentation of the granules varied between the granulations and that the fragmentation propensity of the granules determined the tablet strength. This was explained by assuming that the fragmentation of the granules during compression increased the surface area available for intergranular attraction and thereby increased the tensile strength of the obtained tablets. It seems consequently that there are two main physical properties of granules which appear to be of significant importance for the tablet strength: the distribution of binder within the granules before compaction and the degree of granule fragmentation during compaction.

In an earlier study (Wikberg and Alderborn, 1990), the evaluation of fragmentation of granules during compression of some lactose granulations was discussed. A number of lactose granulations, produced by varying the amount and composition of the solvent during the agglomeration, were used. It was observed that the granules gave tablets with varying air permeability dependent on the process conditions during the agglomeration probably due to variations in the degree of granule fragmentation during compaction. The intention behind this paper was to study the compactibility of these lactose granulations. Thus, the aim is to support further the concept that the degree of granule fragmentation during compaction is important for the mechanical strength of the tablets.

## Materials and methods

*Granulation*

1 kg of lactose ($\alpha$-monohydrate, Ph. Eur., Pharm. Lactose, AB Svenskt Mjölksocker, Sweden) was granulated with polyvinylpyrrolidone (K-25, Roth, F.R.G.) by wet massing in a 7l planetary mixer (Kenwood A717C, U.K.). The granulations were wet and dry screened in an oscillating granulator (Manesty Rotogran Mark III, U.K.) and the size fraction 500–710 $\mu$m was prepared by hand sieving (Retsch, F.R.G.). The concentration of binder was 5% by weight in the dry granulation. 14 granulations of the same composition were produced by varying the amount and the composition of the solvent for the binder during agglomeration (Table 1). Information concerning the granulation procedure has been presented earlier (Wikberg and Alderborn, 1990).

The prepared size fractions were stored in a desiccator at 40% relative humidity for at least 2 days before tableting.

*Compaction and characterisation of tablets*

Tablets were compacted at machine speed, i.e. 30 rpm, in an instrumented single-punch press (Korsch EK 0, F.R.G.) at a maximum upper punch pressure of 150 MPa. The press was equipped with flat-faced punches with a diameter of 1.13 cm. The distance between the punch faces at the lowest position of the upper punch was in all cases 3 mm at zero pressure. For each tablet, a certain amount of granules was weighed on an analytical balance

TABLE 1

*Amount and composition of solvents for the binder*

| Composition of solvent | Amount of solvent (ml) | Denomination of granulation |
|---|---|---|
| Water | 90 | W1 |
| | 120 | W2 |
| | 150 | W3 |
| | 200 | W4 |
| Water/ethanol 50:50 | 90 | WE1 |
| | 120 | WE2 |
| | 150 | WE3 |
| | 200 | WE4 |
| | 250 | WE5 |
| Ethanol | 120 | E1 |
| | 150 | E2 |
| | 200 | E3 |
| | 250 | E4 |
| | 300 | E5 |

and then manually filled into the die. Before each compaction, the die was lubricated with a suspension of 1% by weight of magnesium stearate in ethanol.

The tablets were stored for at least 2 days in a desiccator at 40% relative humidity at room temperature and the diametral compression strength was then measured with an Erweka tester (Erweka TBH 28, F.R.G.). Since the tablets showed approximately normal tensile failure, the tensile strength was calculated (Fell and Newton, 1970). All data presented are the means of ten measurements.

## Results and Discussion

The tensile strength of tablets compacted from all granulations is presented in Fig. 1. The volume of the binder solvent used during the agglomeration was clearly important with a general trend for the tablet strength to increase with increased amounts. However, for the lowest volumes of agglomeration liquid the trend was not found and the tablet strength increased. This was especially marked for granulation WE1 produced with a water-ethanol mixture as binder solvent. The composition of the binder solvent seemed also to affect the tablet strength although the effect was not pronounced. Generally, the ethanol granulations gave tablets with the highest mechanical strength followed by the water granulations, with the lowest tablet strength for the water-ethanol granulations. The finding that the type of binder solvent can affect the compactibility of the granules is in agreement with an earlier study (Alderborn et al., 1987).

In an earlier paper in this series (Wikberg and Alderborn, 1990) the degree of fragmentation of the granules was estimated by air permeability measurements of the tablets. A comparison between those granule fragmentation data and the tablet strength data presented in this paper shows a similar dependence on the type and amount of agglomeration liquid for both these characteristics. In Fig. 2, the tensile strength of the tablets at 150 MPa is therefore presented as a function of the degree of granule fragmentation during compaction. This fragmentation propensity is estimated by, firstly, the slope from the tablet surface area-compaction pressure profile and, secondly, the area under the curve (AUC) from the tablet permeability coefficient-compaction pressure profile.

There is a general trend that a higher tablet strength corresponds to a higher slope value and a lower AUC, i.e. an increased tablet strength with an increased degree of granule fragmentation. The same principal relation between tablet strength and particle fragmentation has previously been

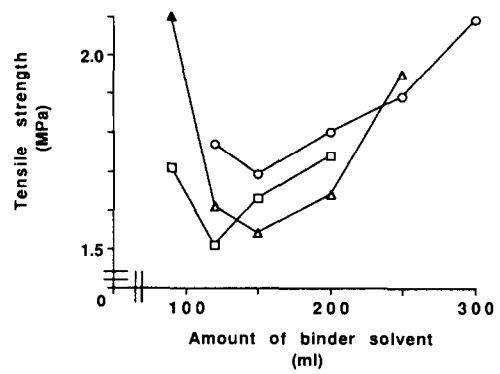


Fig. 1. Tensile strength of tablets as a function of the amount of binder solvent used during the granulation process. (□) W1-4, (△) WE2-5, (▲) WE1, (○) E1-5.

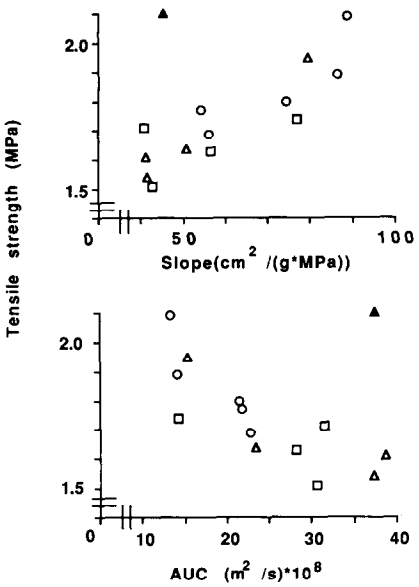


Fig. 2. Tensile strength of tablets as a function of the slope from the tablet surface area-compaction pressure profile (upper panel) and as a function of the area under the curve from the permeability coefficient-compaction pressure profile (lower panel). Symbols as in Fig. 1.

observed for tablets of pure crystalline lactose (Vromans, 1987). However, the relationship was not perfectly linear for these granulations and if the results for granulation WE1 (marked with a filled symbol) are included, there is a marked change in the relationship at the lowest amounts of agglomerating liquid.

During the primary characterisation of the granules (Wikberg and Alderborn, 1990), it was found that the binder content of the granulations produced with ethanol and water-ethanol as solvents tended to increase for the lowest amounts of agglomeration liquids. This was especially marked for granulation WE1. This granulation also showed an unexpectedly low granule friability which supported the observation concerning the amount of binder. It is therefore suggested that the break in the relationship between tablet strength and degree of granule fragmentation as seen in granulation WE1 is a result of the increased binder content. This suggests that the degree of fragmentation of the granules was not greatly affected by such small variations in binder content while the tablet strength, on the other hand, may be more markedly affected. Furthermore, it cannot be excluded that a variation in the amount of agglomeration liquid affects the tendency of the granules to deform during compression. It seems reasonable that such a volume reduction characteristic can promote intergranular attractions and thereby affect the tablet strength. For these granules, the less fragmenting examples should then deform to a larger extent during compression than those fragmenting more and give rise to a non-linear relationship.

The results in this study support earlier findings (Alderborn et al., 1987) that the degree of granule fragmentation is significant for and might determine the tablet strength. This observation can be explained by such a hypothesis and indicates a model which assumes that a tablet compacted of granulated materials consists of granules adhered to each other. Such a model is supported by studies on the pore size distribution (Selkirk and Ganderton, 1970; Carstensen and Hou, 1985) and the appearance, as studied using an SEM technique (Seager et al., 1981), of tablets compacted of granulated materials. If this model is valid, it seems reasonable that the attractions between granules are weaker than the attractions between primary particles within a granule. Thus, the strength of these inter-granular attractions governs the tablet strength. The results thereby indicate that the surface area of the granules in a compact reflects the total inter-granular interaction potential in the tablet. A larger granular surface area, i.e. the external or enveloped surface area of the granules, can possibly increase the total surface area of inter-granular attraction and thereby the tablet strength. Furthermore, the surface area reflects the mean pore diameter in a tablet, i.e. a larger surface area indicates a smaller pore diameter for tablets of similar porosity. The pore diameter can be seen as a measure of the distance between granule surfaces. If this distance is reduced it seems probable that the magnitude or intensity of the interactions increases and this will increase the tablet strength.

The surface of a granule exposed to the surroundings consists probably of both the starting material or substrate, i.e. in this case lactose, and the binder which coats or covers the substrate

particles (Krycer et al., 1983). There are thereby three possible types of interactions between granule surfaces depending on whether or not the substrate particles are coated with the binder (Rowe, 1988). It seems reasonable that the adhesion between binder and substrate or cohesion between binder-coated surfaces is stronger than substrate-substrate cohesion. Consequently, the fraction of the total external granule surface area in the tablet which is binder coated might be of importance for the tablet strength. The distribution of the binder within the granule before compaction as well as the degree and mechanism of fragmentation will probably affect the type of inter-granular attractions. The distribution of the binder in the granules before compaction can be affected by the distribution of the liquid in the powder mass and the wetting of the particles as well as an eventual migration of binder during drying (Ridgway and Rubinstein, 1971). It is also probable that the mechanism of granule fragmentation can affect the relationship between binder-coated and non-binder-coated surfaces available for inter-granular attraction in the tablet. It is possible that the fragmentation of granules can occur by fracturing or cleavage of the primary particles or by a failure between the particles, irrespective of whether binder-coated, or between a particle and the adhered binder. The fracturing of primary particles, especially, can result in a large proportion of non-binder-coated surfaces.

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